Rec'd PCT/PTO 11 MAR 2005
PCT/GB 2003 / 0 0 4 1 3 5

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

RECD 06 NOV 2003
WIPO PCT

PRIORITY DOCUMENT

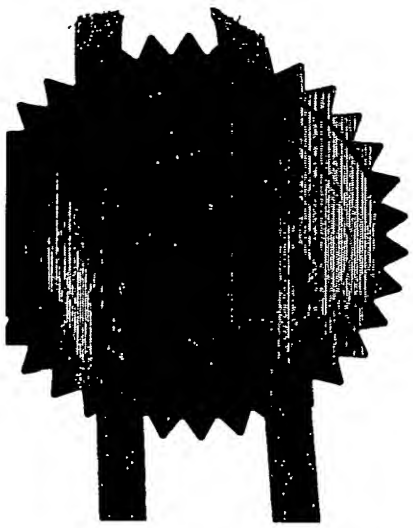
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed P. Mahoney

Dated 22 October 2003

BEST AVAILABLE COPY

atents Form 1/77

Patents Act 1977
(Rule 16)

The **Patent Office**

THE PATENT OFFICE
19 SEP 2002
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet, from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — LB1593

19 SEP 2002

2. Patent application number *(The Patent Office will fill in this part)* — 0221781.8

20SEP02 E749642-1 D02806
P01/7700 0.00-0221781.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Exstent Limited
Royal Brompton Hospital
Sydney Street
London
SW3 6NP

Patents ADP number *(if you know it)* 8468209001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Improvements in or relating to Stents

5. Name of your agent *(if you have one)* — Barker Brettell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

10-12 Priests Bridge
LONDON
SW15 5JE

Patents ADP number *(if you know it)* 7442494003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	10
Claim(s)	5
Abstract	1 DML
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Barker Brettell Date

Barker Brettell 19 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Lance Butler — Tel: 020 8392 2234

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 01645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
e) Once you have filled in the form you must remember to sign and date it.
f) For details of the fee and ways to pay please contact the Patent Office.

DUPLICATE

IMPROVEMENTS IN OR RELATING TO STENTS

[0001] This invention concerns improvements in or relating to stents for use in humans.

[0002] The present invention has particular but not exclusive reference to a stent for use in association with the ascending aorta.

[0003] Aortic dissection is or can be a fatal occurrence since the rupture of the artery occasions dramatic haemorrhaging resulting in system failure. One particular condition afflicting a significant number of people is that known as *Marfan's Syndrome* which affects the connective tissue in the body to the extent that the aortic root becomes a focus for weakening in time with the pulsing of the blood flow from the heart. The tissue of which the artery is made is weakened and accordingly stretches with a concomitant increase in the diameter of the artery giving rise to dissection or aneurysm. The wall of the artery becomes thinner in section and should distension increase further rupture will occur with the results indicated *supra*. In addition, the aortic valve is formed at the base of the aorta and the distension thereof additionally and adversely affects the operational efficiency of the valve with leakage occurring.

[0004] Of course, aortic root dissection is not confined to sufferers of *Marfan's Syndrome* and can affect any one.

[0005] Conventionally the surgical procedures for addressing the problem, either electively or on an emergency basis, involve the insertion of a stent in the aorta or the removal of the aortic root and its replacement with a stent incorporating a mechanical valve, or in some cases a pig's valve, the stent being sutured in place. In an alternative procedure the stent is

inserted within the aortic root, following appropriate incision thereof, which is then sutured back into position. These procedures do, however, involve considerable expenditure in both time and cost. The deployment of a heart/lung bypass machine is required with all the dangers of infection associated with such intrusive procedures. Post-operatively because of the intimate contact between the blood and the now installed internal replacement root and valve combination a continuing risk of infection remains without limit as to time. Patients having undergone such surgery have to be continuously mindful of the need to secure antibiotic protection whenever potentially intrusive activity on the body is contemplate, for example dentistry. Furthermore due to the increased risk of clotting following surgery of this kind anti-coagulants have to be administered usually on a daily basis with blood tests to check the INR being necessary regularly, thus adding to the on-going cost of patient care.

[0006] The conventional stents deployed internally are generally produced from synthetic material one example of which is that available under the trade name *DACRON*®, a polyester with tough elastic properties. In some designs of internal stent reinforcement giving a degree of rigidity coupled with flexibility is provided and may take the form of a spirally wound open-coiled or mesh insert. The flexibility is necessary to accommodate differing tortuosity of arteries, but the rigidity is also required to resist deformation by kinking for example.

[0007] Conventional internal stents for treating aneurysms are available in a range of sizes to fit as appropriate. However the stents do not mould to the internal contours of the distended artery at the point of the aneurysm. The internal stents locate within the artery either side of the aneurysm and accordingly pockets may be formed externally of the stent but within the artery and these pockets may contain blood. In the case of

aortic root replacement by removal of the root and substitution with a stent and valve, the diameter of the stent is chosen to match either the exit aperture in the left ventricle, if the valve is to be replaced, or to the lower section of the artery if the valve is not to be replaced. Accordingly the graft of the stent onto the upper end of the aorta adjacent the aortic arch tends not to be such a good fit.

[0008] An object of the present invention is to provide a new and improved stent that obviates the need for procedures of such an intrusive character as are currently required.

[0009] A further object of the invention is to provide a method of manufacturing the new and improved stent whereby the resultant stent is of customised form.

[0010] According to a first aspect of the present invention there is provided a stent adapted for location exteriorly of a blood vessel, the stent being formed in such manner as to be locatable around and in morphological relationship with the said blood vessel, and means for maintaining the stent in such relationship with the blood vessel.

[0011] The stent may include a sleeve that may be in two parts and of generally cylindrical form but may include one or more sections of varying form in order to conform to the morphological requirements in any particular case.

[0012] The sleeve is provided with appropriately located recesses or apertures for accommodating other interconnecting blood vessels or structures contiguous with the blood vessel being supported by the stent.

[0013] The sleeve of the stent may be provided with a base or flange portion for attachment to a main heart structure, for example the ventricle muscle, such that a securement or anchor point is established for the stent. The base or flange portion may be adapted for appropriate suturing or other means to the said structure. For example the other means may include stapling or adhesion.

[0014] In an alternative form of the stent of the present invention the sleeve may not be required to be secured to the heart structure and may be of such morphological size-matching to the blood vessel as to obviate the need for additional securement. In such event the stent effectively moulds to the shape of the blood vessel, e.g. the ascending aorta, and in this manner provides the necessary support and positive location as required. In one embodiment the stent may be tapered at either end in opposite directions such that when in position on the vessel, the stent locks in position and is thus maintained in its appropriate location.

[0015] The interconnection of the parts of the sleeve may be effected by a hinge mechanism with releasable latches provided at the mating edges of the parts.

[0016] In the alternative, the sleeve may be of resilient material slit longitudinally to allow it to be expanded over the wall of the artery and then to recover its original condition, the sleeve being suitably clampable in position embracing the artery in the said morphological relationship. The clamping may be achieved by the application of suitable ties, for example those known as cable ties which lock firmly around the sleeve, which may be provided with one or more grooves for receiving and locating the ties. The clamping may alternatively be effected by the insertion of a locking pin extendable through hinge elements provided at the mating edges of the slit in the sleeve.

[0017] It will be appreciated that other means of securing together the parts of the stent sleeve may be adopted without departing from the present invention. For example zip fasteners appropriately designed to avoid the presence of surfaces that may snag and provided with suitable means for this purpose. In particular the surface of the fastener in contact with the blood vessel, e.g. the aorta, should be of such character as not to give rise to fretting. In this respect a protective flap could be provided.

[0018] The sleeve of the stent may be of varying thickness with the greatest thickness being provided in the base or flange region thereof to provide strength at the point of attachment. The thickness may therefore reduce away from that region to afford a degree of flexing given the need to accommodate the pulsing of the blood through the artery.

[0019] The sleeve may have an outer casing and a relatively inner casing, the outer casing being of more rigid construction than the inner casing which latter may be configured to provide the flexure mentioned above. In this connection the inner casing may be of petal-like form to encompass the artery but to allow flexing.

[0020] In an alternative embodiment the stent of the present invention is formed of one or more parts of spiral formation whereby when in position around the blood vessel close support is given thereto. An advantage of this embodiment lies in its potential for feeding on to the vessel and reforming into a spirally wound coil to provide a unitary support. In position the spiral formation may form either an open coil or a closed coil and may accordingly constitute a former like structure surrounding the blood vessel. This embodiment may be in one or more sections dependent upon the axial length and form required. Suitable

interconnections for the sections are provided and may be in the form of screw fitments or their equivalent whereby upon tightening the coil embraces and supports the blood vessel.

[0021] The spiral form of stent of the present invention may allow tissue growth within its interstices thereby serving to enhance its integrity in relation to the blood vessel and concomitantly its strength.

[0022] The inner surface of the stent must be of a smoothness to ensure that no fretting or abrasion occurs and for similar reasons the external surface of the stent must equally be tolerant of other adjacent body parts, for example other blood vessels or the pericardial wall.

[0023] The inner surface of the stent may be suitably contoured or profiled to minimise fretting or abrasion and to assist in the egress of metabolites that may issue from the outer surface of the blood vessel into contact with the stent. The inner surface of the stent may in this even assist in the movement of the metabolites into the pericardial space possibly with a peristaltic effect. Further, the contouring or customising of the stent in this fashion assists in restricting axial movement of the blood vessel, e.g. the aorta, tending thereby to ensure the containment of the vessel within the limits of the stent. The stent thus acts as a mechanical barrier to axial as well as diametral movement of the blood vessel.

[0024] The material from which the stent is produced must possess structural integrity in terms of its burst strength, bend strength, tensile strength, liquid porosity, load distribution and general security particularly for mounting to the heart muscle. Further the material should possess a degree of opacity but should be translucent for the purposes of allowing non-intrusive investigative procedures to take place,

for example MRI scanning. The material should, however, be resistant to the effect of electro-magnetic fields.

[0025] The material must also be thermally stable given the potentially variable nature of its working environment and has to be biocompatible in terms of its location within the body structure. In particular, it must possess mechanical, chemical, thermal, proteinal, enzymal and pericardial fluid biocompatibility and resistance to attack from any of these sources.

[0026] The material from which the stent may be made may contain antibiotics gradually releasable in time, the antibiotic elements being incorporated during the manufacture of the stent.

[0027] The material from which the stent may be made may be polymeric, metallic, or ceramic or appropriate mixtures thereof to meet the requirements of strength and compatibility hereinbefore mentioned. Another material that may be appropriate is a heat shrink plastics material that would be recoverable in terms of shape either immediately or over a period of time to produce the morphological fit, which is an important novel and inventive step of the present invention. The recovery of the plastics material may be in-built such that it occurs over a period of time or in the alternative the recovery could be triggered by appropriate external means.

[0028] In general the stent of the invention may be of such form as to be adjustable following its initial application to the affected blood vessel. Such adjustment may be capable of initiation externally of the patient's body and may be electronic.

[0029] According to a second aspect of the invention there is provided a method of manufacturing a stent according to the first aspect for

morphologically fitting an artery including the steps of producing a computerised 3D model from a scanned image of the artery to which the stent is in practice to be applied, and rapid prototyping the computerised 3D model in an appropriate material to provide the stent or a mould for the stent or a precursor therefor.

[0030] (A further method of producing the stent includes the steps of opening the thorax of the patient, the applying a polymeric wrap by hand to an approximate fit around the blood vessel and thermally treating the wrap to fix it in situ to the shape of the vessel, and closing the thorax.

[0031] (A still further method of producing the stent includes the steps of opening the thorax and the pericardium, applying shuttering to the blood vessel, injecting room temperature vulcanising (RTV) or room temperature curing polymer around the blood vessel and within the shuttering, allowing the setting of the polymer, removing the shuttering and closing the thorax.

[0032] A third aspect of the invention is a stent made in accordance with the method.

[0033] The scanned image may be generated for example from an MRI procedure applied to the affected artery of the patient and is then computerised and converted into a stent design. Other investigative procedures may be adopted for the initial imaging step, for example MRA, X-ray CT, 3D pulsed Doppler Echo measuring, namely a 3D version of 2D echocardiography used for aortic root measurement, and any other appropriate imaging technique. Suitable CAD software is employed to create the requisite customised 3D model of the affected artery and this image is then utilised for the rapid prototyping stage. The rapid prototyping, conventionally known in its abbreviated form as

'RP', is conducted on a suitable machine in which is produced in a suitable material a three-dimensional reproduction of the CAD image. The RP reproduction may give the actual stent or may provide the model from which the stent may be produced. In this latter respect, the model may be used to generate a mould from which the stent may be produced, in a similar vein to the 'lost wax' process. In either case the stent so generated is customised for the individual patient and contrasts sharply with the current procedures using internally applied stents of stock sizes.

[0034] The RP method may employ Stereo Lithography (SLA), Selective Laser Sintering (SLS Solid ground curing (SOLIDER) 'Laminated object manufacturing (LOM) Fused deposition modelling (FDM) or Computer Numerical Controlled (CNC) machining for producing the stent.

[0035] The stent of the invention conforms morphologically to the contours of the affected artery and when applied effectively provides a clamped sleeve to support its exterior in substantially full contact therewith. In the case of an aortic root the clamping of the sleeve also provides an adjustment for the aortic valve in terms of repositioning the valve seat to reinstate or reinforce integrity to prevent leakage at this location, thus avoiding the need to replace the valve.

[0036] The present invention does not require the high degree of invasive surgery associated with conventional surgical procedures for aortic root resection and valve replacement. Importantly also when the stent is in place although clearly it is in contact with bodily fluids and internal features of the pericardium and neighbouring parts, its external nature means that it is not in contact with blood. This very facet of the invention is of high benefit in terms of avoiding the possibility of infection affecting the blood stream and also obviates or significantly reduces the dependency of the patient, having undergone the successful

procedure, on-after care and drugs and treatment associated therewith. Quite apart from these advantages the avoidance of such invasive surgery is clearly less traumatic for the patient.

[0037] Beating heart surgery thus becomes a possibility by virtue of the present invention which provides a bespoke stent. Indeed with some forms of the stent, for example the spirally wound version, the opportunity arises for keyhole surgery with all the attendant advantages which that offers in terms of non-intrusive procedures with less patient trauma and post-operative care and medication.

[0038] It will be appreciated that whilst the present invention has been described principally with reference to aortic root resection, it has a wider applicability generally to the treatment of aneurysms in any blood vessel and accordingly any reference herein to 'arteries' is to be construed in the wider context of blood vessels generally.

CLAIMS

1. A stent adapted for location exteriorly of a blood vessel, the stent being formed in such manner as to be locatable around and in morphological relationship with the said blood vessel, and means for maintaining the stent in such relationship with the blood vessel.

2. A stent according to Claim 1 in which the stent is in the form of a sleeve in at least two parts, the sleeve being of generally cylindrical form.

3. A stent according to Claim 2 in which the sleeve includes one or more sections of varying form in order to conform to the morphological requirements in any particular case.

4. A stent according to any one of the preceding claims in which the sleeve is provided with appropriately located recesses or apertures for accommodating other interconnecting arteries.

5. A stent according to any one of the preceding Claims 2 to 4 in which the sleeve of the stent is provided with a base or flange portion for attachment to a main heart structure, for example the ventricle muscle, such that a securement or anchor point is established for the stent, the base or flange portion being adapted for appropriate attachment to the said structure.

6. A stent according to any one of the preceding claims 2 to 5 in which the interconnection of the parts of the sleeve is effected by a hinge mechanism with releasable latches provided at the mating edges of the parts.

7. A stent according to any one of the preceding Claims 2 to 4 in which the sleeve is of resilient material slit longitudinally to allow it to be expanded over the wall of the artery and then to recover its original condition, the sleeve being suitably clampable in position embracing the artery in the said morphological relationship.

8. A stent according to Claim 7 in which the clamping is achieved by the application of suitable ties.

9. A stent according to Claim 8 in which the sleeve is provided with one or more grooves for receiving and locating the ties.

10. A stent according to Claim 7 in which the clamping is effected by the insertion of a locking pin extendable through hinge elements provided at the mating edges of the slit in the sleeve.

11. A stent according to Claim 5 and any claim dependent thereon in which the sleeve of the stent is of varying thickness with the greatest thickness being provided in the base or flange region thereof.

12. A stent according to Claim 11 in which the thickness reduces away from the base or flange region to afford a degree of flexing given the need to accommodate the pulsing of the blood through the artery.

13. A stent according to any one of the preceding claims 2 to 12 in which the sleeve has an outer casing and a relatively inner casing, the outer casing being of more rigid construction than the inner casing which latter is configured to provide flexure.

14. A stent according to Claim 13 in which the inner casing is of petal-like form to encompass the artery but to allow flexing.

15. A stent according to Claim 1 including at least one spiral part adapted in use to locate over and coil around the blood vessel to provide in position the morphological relationship with the blood vessel.

16. A stent according to Claim 15 in which each spiral part is provided with interengaging means for connection to an adjacent part.

17. A stent according to Claim 16 in which the interengaging means is a screw connection adapted to tighten the coil around the blood vessel.

18. A stent according to any one of Claims 15 to 17 in which in position around the blood vessel the spiral part forms an open coil or a closed coil.

19. A stent according to any one of the preceding claims in which the inner surface of the stent is of a smoothness to ensure that no fretting or abrasion occurs and the external surface of the stent is tolerant of other adjacent body parts.

20. A stent according to any one of the preceding claims in which the material from which the stent is produced is translucent for the purposes of allowing non-intrusive investigative procedures to take place.

21. A stent according to any one of the preceding claims in which the material from which the stent is produced is resistant to the effect of electro-magnetic fields.

22. A stent according to any one of the preceding claims in which the material from which the stent is produced is thermally stable and is biocompatible.

23. A stent according to any one of the preceding claims in which the material from which the stent is made contains antibiotics gradually releasable in time, the antibiotic elements being incorporated during the manufacture of the stent.

24. A stent according to any one of the preceding claims in which the material from which the stent is made is polymeric, metallic, or ceramic or appropriate mixtures thereof.

25. A stent according to any one of the preceding claims in which the material from which the stent is made is a heat shrink plastics material recoverable in terms of shape either immediately or over a period of time to produce the morphological fit.

26. A stent according to any one of the preceding claims in which the size of the stent is adjustable in situ.

27. A stent substantially as hereinbefore described.

28. A method of manufacturing a stent for morphologically fitting a blood vessel according to any one of the preceding claims, the method including the steps of producing a 3D computerised model from a scanned image of the blood vessel to which the stent is in practice to be applied, and rapid prototyping the computerised 3D model in an appropriate material to provide the stent or a mould for the stent or a precursor thereof for morphologically matching the blood vessel.

29. A method according to Claim 28 in which the scanned image is obtained from a procedure selected from the following: MRI, MRA, X-ray CT, 3D pulsed Doppler Echo imaging or an equivalent of any one of the foregoing.

30. A method according to Claim 28 or 29 in which the computerised 3D model is generated using computer-aided design software.

31. A method according to any one of the preceding Claims 28 to 30 in which the computerised 3D model is employed in the rapid prototyping step to generate the stent in the form substantially in which it is to be deployed in a surgical procedure.

32. A method according to any one of the preceding Claims 28 to 30 in which the computerised 3D model is employed in the rapid prototyping step to generate a precursor to the stent, a mould is taken of the precursor, and the stent is then formed in the mould.

33. A method of manufacturing a stent substantially as hereinbefore described.

34. A stent produced by the method according to any one of the preceding Claims 28 to 33.

ABSTRACT OF THE INVENTION

IMPROVEMENTS IN OR RELATING TO STENTS

A stent is provided for external application to an artery in which an aneurysm has occurred or is about to occur to provide support thereto, the stent being of bespoke character by virtue of its creation to conform morphologically to the actual contour of the artery captured using for example MRI, CAD and RP.